PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

LEONARD et al.

Application No.: 09/512,701 Group Art Unit: 1645

Filed: February 25, 2002 Examiner: N. M. Minnifield

For: USE OF IL-12 ANTAGONISTS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

#18
linda
11/5/02

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

RESPONSE

This paper replies to the Office Action issued by the U.S. Patent and Trademark Office on July 16, 2002. Claims 16-31 are pending in this application. Claims 16-31 have been rejected. Applicants thank the Examiner for entering the previous amendment.

Claim Rejections Under 35 U.S.C. § 103(a)

The Examiner rejected claims 16-29 as allegedly obvious over *Gately et al.* (U.S. Patent No. 5,650,492) in view of *Trinchieri et al.* (*Progress in Growth Factor Research*, Vol. 4:355-368, 1992). The Examiner alleges that "since the art teaches the concept that a block in the production of IFN-gamma production would be a means/therapy for the treatment of RA for example (a disease whose pathology is considered to be

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caused by an increase in IFN-gamma) and that IL-12 induces IFN-gamma, it would have been obvious . . . to use the teachings of the prior art as set forth above with the expected benefit of developing a method of using an IL-12 antagonist (anti-IL-12), to block IL-12 which in turn decreases the production of IFN-gamma to treat RA in humans or any other condition that is promoted by an increase in levels of IFN-gamma." Office Action, at 3-4. In general, the Examiner contends that "[b]locking the production of IFN-gamma by using an IL-12 antagonist, would have been a reasonable method for the treatment of RA." *Id.* at 4.

In this obviousness rejection, the Examiner has attempted to use *Gately et al.*, instead of *Feldmann et al.* (as in the previous Office Action of January 29, 2002), to establish an alleged role of IL-12 or IL-12 antagonists in rheumatoid arthritis. However, *Gately et al.* fail to compensate for the inability of *Feldmann et al.* (either alone or in combination with *Trinchieri et al.*) to teach or suggest a method of treating rheumatoid arthritis with an IL-12 antagonist that binds with IL-12.

Gately et al. describe the binding characteristics of IL-12 and its subunits. In particular, they report that the p40 subunit of IL-12 binds to the IL-12 receptor but fails to induce a biological response, and thus acts as a competitive inhibitor. Based on these data, *Gately et al.* conclude that p40 is an IL-12 antagonist, and speculate that it "should be useful in the treatment of disorders such as rheumatoid and other inflammatory arthritides, Type I diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, septic shock, etc." *Gately et al.*, column 4, lines 4-7. This reference discloses

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therapeutic uses of a single protein competitive-inhibitor type of antagonist (i.e., p40) that binds to the IL-12 receptor.

In contrast, the present claims are directed to therapeutic uses of antibodies (not proteins) that bind to IL-12 itself (and not the IL-12 receptor). There is no teaching or suggestion in *Gately et al.* that would lead one of ordinary skill in the art to use an antagonist other than one targeted to the IL-12 receptor. *Gately et al.* do not teach or suggest even other competitive inhibitors of IL-12 binding, much less suggest any other antagonists to IL-12 activity, such as IL-12 antibodies that operate using a different mechanism. Thus, *Gately et al.* do not provide either a motivation to use IL-12 antibodies or a reasonable expectation of success in using them. Both of these requirements must be satisfied for an obviousness rejection. MPEP § 2143. Merely because this was accomplished by the present inventors is of no significance, as hindsight cannot compensate for the lack of motivation or reasonable expectation of success. *Id.*

Gately et al. seem satisfied with their strategy of administering IL-12 protein subunits as antagonists of IL-12. *Gately et al.* do not present any significant disadvantages to their methods and thus do not provide the person of ordinary skill in the art with a motivation to combine the teachings of *Gately et al.* with any other references. See *Winner Int'l Royalty Corp. v. Wang*, 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000) (requiring that apparent disadvantages exist before a motivation to combine could stem from the nature of the problem, as without any disadvantages no problem could be perceived.)

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Trinchieri et al. do not compensate for the deficiency in *Gately et al.* *Trinchieri et al.* investigate the role of IL-12 in an immune response against bacterial infection, and conclude that "this cytokine offers promising possibilities for therapeutical use." *Trinchieri et al.*, at 356. *Trinchieri et al.*, thus, suggest treating patients with IL-12 itself. They use IL-12 antibodies as a tool to demonstrate the role of IL-12 in inducing an immune response and, specifically, in fighting bacterial infections. This reference does not teach or suggest the use of IL-12 antagonists. More importantly, this reference does not teach or suggest the use of IL-12 or IL-12 antibodies in treating autoimmune disorders. In fact, instead of teaching inhibition of IL-12 activity, this reference suggests administering IL-12 to enhance an immune response (e.g., during the treatment of HIV-induced immunosuppression and consequent bacterial infections). *Trinchieri et al.*, at 365-6. Thus, *Trinchieri et al.* do not compensate for the deficiencies in the teachings of *Gately et al.* Additionally, *Trinchieri et al.*, as it does not even discuss rheumatoid arthritis, provides no motivation to combine the references, or reasonable expectation of success in a combination.

In summary, it is clear from the above discussion that the cited prior art references fail to teach or suggest all the claim elements when taken alone or together, fail to provide suggestion or motivation to modify or combine teachings, and fail to provide a reasonable expectation of success. Therefore, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness. At best, the Examiner has proposed an "obvious to try" scenario that is not a proper basis for an obviousness rejection.

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In response to the previous Office Action, Applicants argued that the rejection over *Feldmann et al.* and *Trinchieri et al.* failed because *Feldmann et al.* describes the use of anti-TNF-α antibodies to block TNF-α in a murine collagen-induced model of disease. Based on their findings, *Feldmann et al.* identify TNF-α as an important target in rheumatoid arthritis, and they suggest that their results do not exclude the possibility that blocking other cytokines may yield similar results. They list a number of cytokines that are either stimulated or induced by TNF-α. However, they fail to teach or suggest any role for IL-12 or IL-12 antagonists. More importantly, *Feldmann et al.* fail to teach or suggest a method for treating rheumatoid arthritis in a human subject comprising administering to said subject a therapeutically-effective amount of an IL-12 antagonist that binds with IL-12, as presently claimed. Applicants respectfully submit that the substitution of the *Gately* reference instead of the *Feldmann* reference has not remedied the deficiencies in the prior rejection. Although *Gately et al.* teach that the p40 subunit of IL-12 can act as an antagonist (i.e., by binding to the IL-12 receptor), and may be useful in treating rheumatoid arthritis, they fail to teach or suggest the use of any antagonist that directly targets IL-12 protein. In fact, unlike *Feldmann*, *Gately* does not even discuss the antibody art. Therefore, Applicants contend that the current rejection still does not render the claimed invention obvious because the Examiner still lacks a proper motivation to combine the references and a reasonable expectation of success in using the antibodies to treat rheumatoid arthritis. Applicants request that the Examiner withdraw this rejection.

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Claim Rejections Under 35 U.S.C. § 112

The Examiner rejected claims 23, 24, 30, and 31 under 35 U.S.C. § 112, first paragraph. The Examiner acknowledges that the specification is enabling for a method of using an IL-12 antibody to treat rheumatoid arthritis. However, she alleges that the specification fails to enable a method of using an antibody that binds to a 40 kD or 35 kD subunit of IL-12. Applicants respectfully submit that there is support in the specification for the use of antibodies to the 40 kD and 35 kD subunits of IL-12 to treat rheumatoid arthritis as follows:

> Another form of IL-12 which may be used in the present invention is an IL-12 subunit capable of treating the desired autoimmune condition in a mammalian subject. Such an IL-12 40 kD subunit has substantial homology to the human IL-12 40 kD subunit disclosed in PCT/US91/06332, and such an IL-12 35 kD subunit has substantial homology to the human IL-12 35 kD subunit disclosed in such PCT application.

Specification, at 8, lines 13-20.

> Autoimmune conditions which are promoted by an increase in levels of IFN-γ and/or TNF-α include, without limitation, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes melitis and autoimmune inflammatory eye disease.

Id. at 6, lines 16-20.

In addition, Applicants submit that there are teachings in the specification for the preparation of IL-12 antibodies, including those produced by inoculation of a mammalian subject with IL-12 or IL-12 fragments. *Id.* at 7, lines 12-19. Support for using these antibodies is also provided. *Id.* at 13-14. It is well-established that IFN-γ

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promotes several autoimmune conditions including multiple sclerosis and rheumatoid arthritis. Therefore, the ability IL-12 antagonists to decrease IFN-γ production and symptomatology in one or more related autoimmune conditions (including well-established animal models) can be used as the basis for designing IL-12 antagonist-based therapy of similar autoimmune conditions. The specification provides an example of how IL-12 antibody can be used to treat an animal model of multiple sclerosis, showing that it does, in fact, decrease levels of IFN-γ production. *Id.* at 14-21. Applicants contend that one skilled in the art would be able to use this invention as disclosed, and optimize it with undue experimentation, to treat rheumatoid arthritis, another condition that benefits in a reduction of IFN-γ levels.

Lastly, the Examiner alleges that the specification is not enabling for the method of treating rheumatoid arthritis using IL-12 antagonists in combination with other therapies for autoimmune conditions, and therapies for autoimmune conditions comprising steroidal or other anti-inflammatory therapies. Applicants respectfully submit that there is support in the specification for these claims (30-31) as follows:

> The IL-12 antagonist or IL-12 used in practicing the present invention may be administered alone or combined with other therapies for autoimmune conditions, such as steroidal or other anti-inflammatory therapies and administration of other cytokines.

Id. at 14, lines 9-11.

In addition, Applicants advise that these therapies for autoimmune conditions were known to be useful before the date of this invention. In fact, combination therapy for rheumatoid arthritis involving steroids, nonsteroidal anti-inflammatory drugs,

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cytokines, and antibodies was well-established in the early 1990's. *van der Veen et al.*, Clin. Rheumatol., 12:500-505 (1993); *Jaffe*, J. Rheumatol. Suppl., 25:24-27 (1990); *Wilske*, Br. J. Rheumatol., 32 Suppl. 1:24-27 (1993);*Vitali et al.*, Int. J. Artif. Organ, 16 Suppl. 5:196-200 (1993). Therefore, the skilled artisan or physician would be able to use IL-12 antagonists in combination with other therapies without undue experimentation. Accordingly, Applicants request that the Examiner withdraw this rejection.

Conclusion

In view of the foregoing remarks, Applicants submit that this claimed invention is neither anticipated nor rendered obvious in view of the prior art references cited against this application. In addition, Applicants submit that the claims are fully enabled by the specification. Applicants therefore respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims. Should the Examiner not believe that the claims are in condition for allowance, Applicants request that she please contact their undersigned representative at (202) 408-4086 for an interview to discuss the application.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
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1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: October 16, 2002

By: Rebecca M. McNeill
Rebecca M. McNeill
Reg. No. 43,796

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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